PSJ2 Exh 18

OxyContin® Controlled Release Tablets
NDA #20-553

ADVERTISING REPORT [Single Product]

Submission Date: November 13, 2003

[RA Archive File Copy - Volume 1 of 1]

Purdue Pharma L.P.
Stamford, CT

Note: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUMBITTED: November 13, 2003 *[Page 1 of 2]*

2. LABEL REVIEW NO. *(Biologics)*

Form Approved: OMB No. 0910-0376
Expiration Date: October 31, 2004
See OMB Statement on Reverse Part 1

3. NDA/ANDA/AADA OR BLA/PLA/PMA
Number: **20-553**
Single product ☒ Multiple products ☐

4. PROPRIETARY NAME	5. ESTABLISHED NAME	6. PACKAGE INSERT DATE and ID NO *(Latest final printing labeling)*	7. MANUFACTURER NAME:
OxyContin® 10, 20, 40, 80 and 160 mg Tablets	**oxycodone hydrochloride** Prod. Code No.	**Version No. #OT00367D-E dated 7/30/03**	**Purdue Pharma L.P.** License No. *(Biologics)*

FDA/CBER USE ONLY

REVIEWED BY:	DATE	RETURNED BY:	DATE

8. ADVERTISMENT / PROMOTIONAL LABELING MATERIALS

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
PEP	10/28/03	*Artwork No. A7090-P1* OxyContin® 2003 Convention Panel: "There Can Be Life with Relief" (Picnic)	n/a	
PEP	10/28/03	*Artwork No. A7090-P2* OxyContin® 2003 Convention Panel: "There Can Be Life with Relief" (Picnic)	n/a	
PEP	10/28/03	*Artwork No. A7090-P3* OxyContin® 2003 Convention Panel: "There Can Be Life with Relief" (Picnic)	n/a	
PPO	10/15/03	*No. Artwork No. or Job No.* Purdue's Letter to the Editor of Newsweek Magazine Regarding the 10/20/03 Cover Story about OxyContin®	n/a	
PPO	11/3/03	*Job No. OOR350* Drug Identification Chart of "Abused Pharmaceutical Substances" by the National Association of Drug Diversion Investigators (NADDI)	n/a	
PPR	10/13/03	*No Artwork No. or Job No.* Press Release dated 10/13/03, entitled "Tamper-Resistant Prescription Pads Offered to Michigan Physicians to Help Reduce Prescription Drug Diversion"	n/a	

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Beth Connelly
Manager, U.S. Regulatory Affairs

10. SIGNATURE OF RESPONSIBLE OFFICIAL
[SIGNATURE APPEARS ON PAGE 2 OF THIS FORM]

11. APPLICANT'S RETURN ADDRESS
Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(203) 588-7289
b. FAX NO.
(203) 588-6229

13. BIOLOGICAL PRODUCTS: *(Check One)*
☐ Part I/Draft ☐ Part II/Final

FORM FDA 2235 (10/01)

Created by: PSC Media Arts Branch (301) 443-2454 EF

Note: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUMBITTED: November 13, 2003 *[Page 2 of 2]*

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Single product ☒ Multiple products ☐

4. PROPRIETARY NAME	5. ESTABLISHED NAME	6. PACKAGE INSERT DATE and ID NO *(Latest final printing labeling)*	7. MANUFACTURER NAME:
OxyContin® 10, 20, 40, 80 and 160 mg Tablets	**oxycodone hydrochloride** Prod. Code No.	**Version No. #OT00367D-E dated 7/30/03**	**Purdue Pharma L.P.** License No. *(Biologics)*

FDA/CBER USE ONLY

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Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
PSA	10/29/03	*Artwork No. D7072* OxyContin® Visual Aid: "There Can Be Life with Relief"	n/a	
WWW	4/17/03	*No. Artwork No. or Job No.* Site Navigation for OxyContin® Information in "Newsroom" of Purdue's Corporate Website	n/a	
PCT	9/9/03	Current Purdue Wholesaler Pricing Schedule for OxyContin®	n/a	

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Beth Connelly
Manager, U.S. Regulatory Affairs

10. SIGNATURE OF RESPONSIBLE OFFICIAL
Beth Connelly

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13. BIOLOGICAL PRODUCTS: *(Check One)*
☐ Part I/Draft ☐ Part II/Final

FORM FDA 2235 (10/01)

Created by: PSC Media Arts Branch (301) 443-2454 EF

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL EXHIBIT PANEL ("PEP")

OxyContin® 2003 Convention Panel:
"There Can Be Life with Relief" (Picnic)

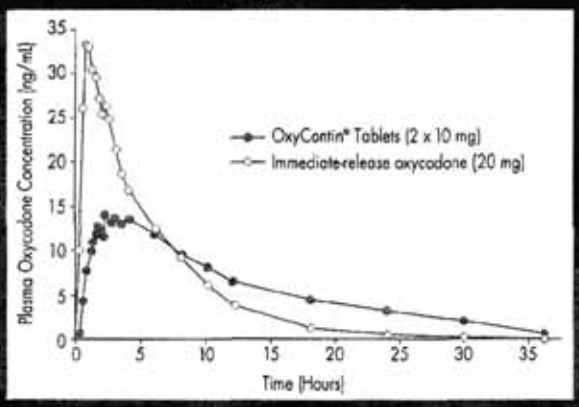
Artwork No. A7090-P1

Implementation Date: 10/28/03

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

Less fluctuation in plasma concentrations

Mean plasma concentrations of oxycodone in normal volunteers after single doses of OxyContin® Tablets and immediate-release (IR) oxycodone[1]



- In a study comparing 10 mg of OxyContin® every 12 hours to 5 mg of IR oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations
- Less fluctuation in plasma concentrations with OxyContin® than with immediate-release oxycodone

- **OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.** Consider this when an increased risk of misuse, abuse, or diversion is a concern
- OxyContin® Tablets are **NOT** intended for use as a prn analgesic
- **OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE**
- **OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablets may cause fatal respiratory depression when administered to opioid-naive patients
- The most serious risk with OxyContin® is respiratory depression, which can be fatal
- As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort
- OxyContin® is not indicated for pre-emptive analgesia, pain in the immediate postoperative period (the first 12 to 24 hours following surgery) in patients not previously taking OxyContin® (because its safety in this setting has not been established), or pain that is mild or not expected to persist for an extended period of time

Reference: 1. [illegible]

Please read professional prescribing information, including boxed warning, available at this exhibit.

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL EXHIBIT PANEL ("PEP")

OxyContin® 2003 Convention Panel:
"There Can Be Life with Relief" (Picnic)

Artwork No. A7090-P2

Implementation Date: 10/28/03

THERE CAN BE LIFE WITH RELIEF

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

Less fluctuation in plasma concentrations

Mean plasma concentrations of oxycodone in normal volunteers after single doses of OxyContin® Tablets and immediate-release (IR) oxycodone*

*In a study comparing 10 mg of OxyContin® every 12 hours to 5 mg of IR oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max} and similar for C_{min} (trough) concentrations.

•Less fluctuation in plasma concentrations with OxyContin® than with immediate-release oxycodone

•OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Consider risk when an increased risk of misuse, abuse, or diversion is of concern

•OxyContin® Tablets are **NOT** intended for use as a prn analgesic

•OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED, TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE

•OxyContin® 80 mg and 160 mg tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablets may cause fatal respiratory depression when administered to opioid-naive patients

•The most serious risk with OxyContin® is respiratory depression, which can be fatal

•As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort

•OxyContin® is not indicated for preoperative analgesia and is not the immediate postoperative period (the first 12 to 24 hours following surgery) as patients not previously taking OxyContin® because its safety in this setting has not been established. In pain that is mild or not expected to persist for an extended period of time

Please read professional prescribing information, including boxed warning, available at this exhibit.

TRANSMITTAL OF ADVERTISEMENTS
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Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL EXHIBIT PANEL ("PEP")

OxyContin® 2003 Convention Panel:
"There Can Be Life with Relief" (Picnic)

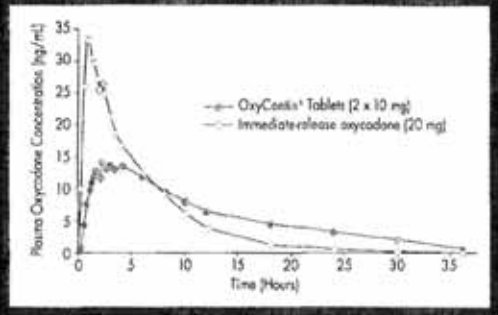
Artwork No. A7090-P3

Implementation Date: 10/28/03

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

Less fluctuation in plasma concentrations

Mean plasma concentrations of oxycodone in normal volunteers after single doses of OxyContin® Tablets and immediate-release (IR) oxycodone[1]



- In a study comparing 10 mg of OxyContin® every 12 hours to 5 mg of IR oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations
- Less fluctuation in plasma concentrations with OxyContin® than with immediate-release oxycodone

- **OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.** Consider this when an increased risk of misuse, abuse, or diversion is a concern
- OxyContin® Tablets are **NOT** intended for use as a prn analgesic
- **OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE**
- **OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablets may cause fatal respiratory depression when administered to opioid-naive patients
- The most serious risk with OxyContin® is respiratory depression, which can be fatal
- As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort
- OxyContin® is not indicated for pre-emptive analgesia, pain in the immediate postoperative period (the first 12 to 24 hours following surgery) in patients not previously taking OxyContin® (because its safety in this setting has not been established), or pain that is mild or not expected to persist for an extended period of time

References: 1. Moolchan JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. Br J Clin Pharmacol. 1996;42:747-756.

Please read professional prescribing information, including boxed warning, available at this exhibit.

THERE CAN BE LIFE WITH RELIEF[IN]

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL PRINT - OTHER ("PPO")

Purdue's Letter to the Editor of Newsweek Magazine Regarding the 10/20/03 Cover Story about OxyContin®

No Artwork No. or Job No.

Implementation Date: 10/15/03

Final – 10/15/03

(Lisa.Miller@newsweek.com, Claudia.Kalb@newsweek.com)

To the Editor:

I was very disappointed that *Newsweek* would reduce the complex medical issue of prescription drug abuse ("In the Grip of a Deep Pain," 10/20/03) to a single tabloid headline – "The Scourge of OxyContin" – on the cover of the magazine. A colleague and I spent more than two hours last Friday night explaining the science and providing background information on this issue to Claudia Kalb, who seemed to understand the context. The article itself was relatively accurate and balanced. Nevertheless, by resorting to tabloid journalism on the cover, *Newsweek* has helped to perpetuate the "urban myth" that OxyContin abuse is somehow different from the abuse of dozens of other medications, which are misused by an estimated 4 million Americans every month.[1] Sensational headlines like these cause unnecessary anguish to millions of legitimate patients.

Newsweek should serve as a voice of balance and facts, not sensational innuendo. Instead, your headline writer incorrectly characterized Mr. Limbaugh's problem. It has not been reported that Rush Limbaugh said he was addicted to OxyContin – he admitted that he was addicted to "painkillers." OxyContin is only one of a number of painkillers that have been implicated in his unfortunate situation. Regardless, all of these controlled substances are abused, and yet you chose to focus only on one medicine in your headline rather than acknowledge the complexity of the truth.

I think you owe an apology to the millions of patients who suffer from debilitating pain and rely on medications like OxyContin. They have been stigmatized enough.

Paul D. Goldenheim, MD
Executive Vice President, Worldwide Research and Development
Chief Scientific Officer

The professional product labeling for OxyContin® Tablets contains the following **boxed warning:**

[1] National Institute on Drug Abuse, Research Report Series, Prescription Drugs: Abuse and Addiction, http://www.nida.nih.gov/researchreports/prescription/prescription5.html.

WARNING:
OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.
Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
OxyContin Tablets are NOT intended for use as a prn analgesic.
OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.
OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Full prescribing information for OxyContin is available at http://www.purduepharma.com/PRESSROOM/PI/OXYCONTIN_PI.PDF.

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DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL PRINT - OTHER ("PPO")

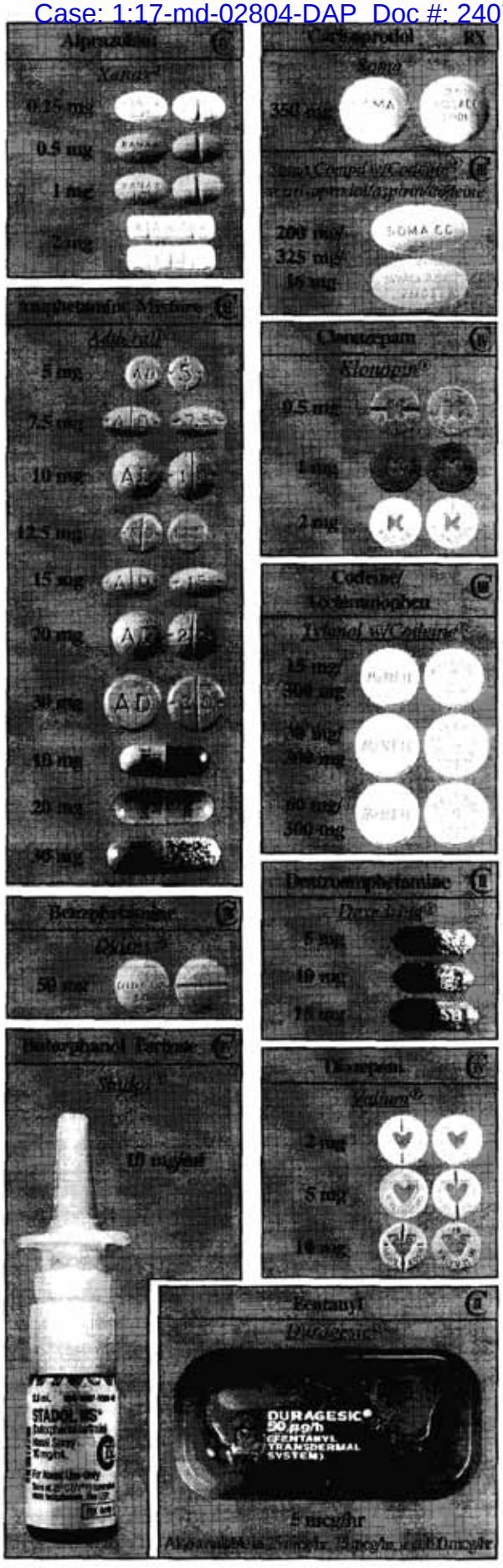
Drug Identification Chart of "Abused Pharmaceutical Substances" by the National Association of Drug Diversion Investigators (NADDI)

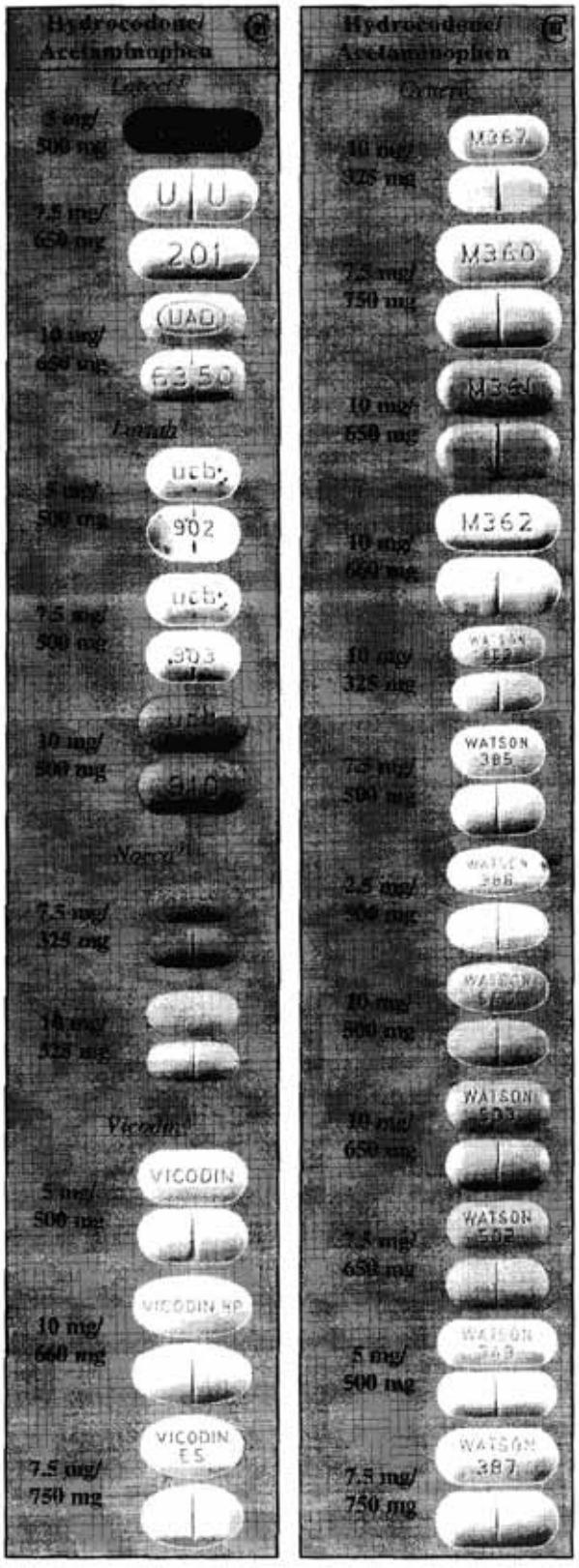
Job No. OOR350

Implementation Date: 11/3/03

Abused Pharm

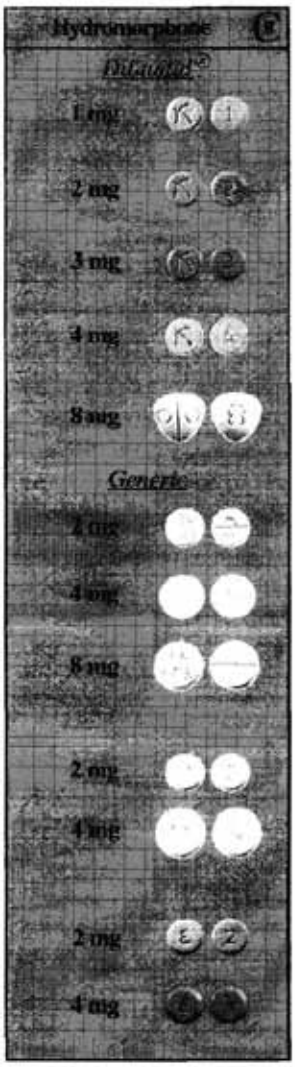
National

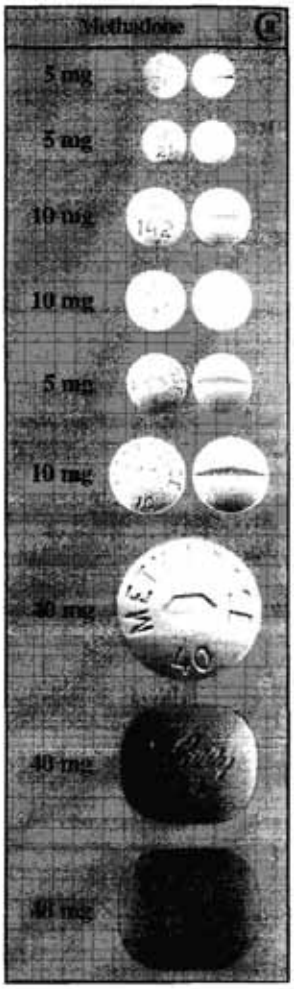


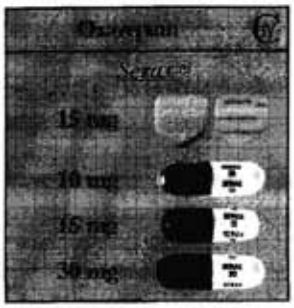


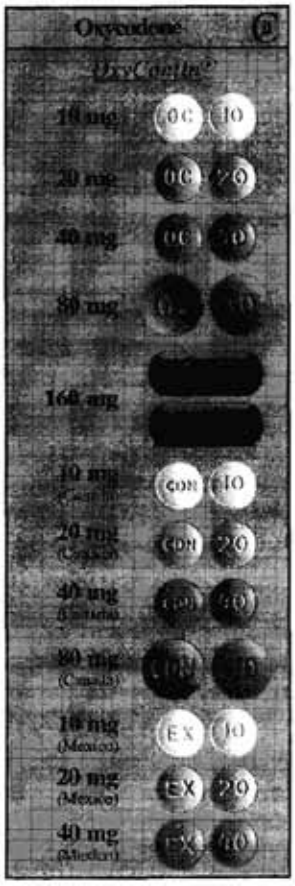
maceutical Substances

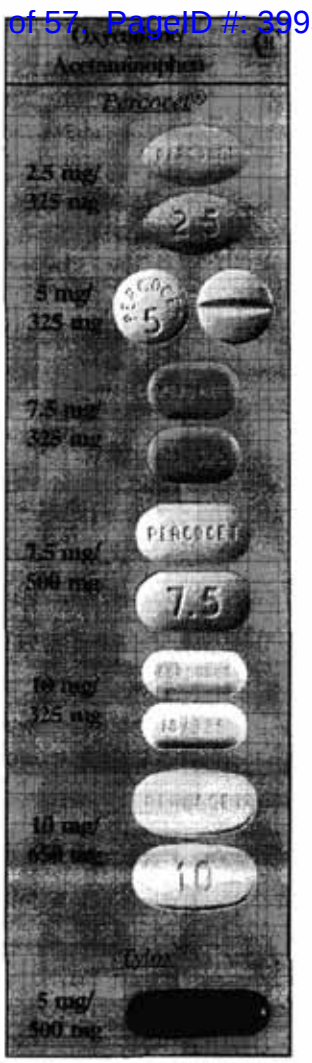
Association of Drug Diversion Investigators, Inc.
1-888-39NADDI www.naddi.org

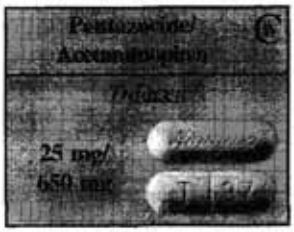


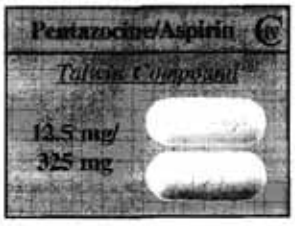


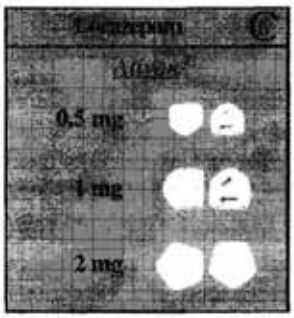


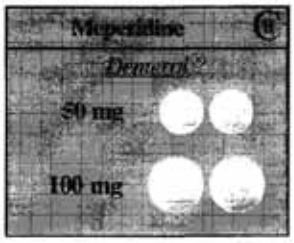


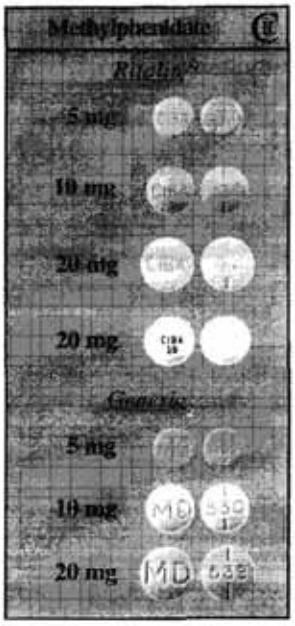












Abused Pharmaceutical Substances

National Association of Drug Diversion Investigators, Inc.

Established in 1987, the National Association of Drug Diversion Investigators, Inc. (NADDI) is a unique membership organization whose members are responsible for investigating and prosecuting pharmaceutical drug diversion. The organization has proven to be a valuable asset to law enforcement, the pharmaceutical industry and health regulatory personnel. NADDI's objective is simple: to improve the members' ability to investigate and prosecute pharmaceutical drug diversion.

NADDI's principle activities comprise: (1) cooperative education and training in the specifics of pharmaceutical drug diversion, investigation, prosecution and prevention; (2) the sharing of investigative information and communication with a wide variety of interested parties with regard to the nature, scope and impact of pharmaceutical drug diversion; and (3) the development of more effective measures to combat the problem.

Information on membership in NADDI can be obtained at our website at www.naddi.org. NADDI conducts a national training conference, and several regional conferences across the United States. Further information is available by contacting one of the NADDI officers through the "Contacts" link on the website, or by calling 1-888-39NADDI.

The National Association of Drug Diversion Investigators has made extensive efforts to feature the top prescription drugs of abuse in this brochure. However, because of the vast array of generic drugs, it is impossible to display all of the pill possibilities. Law enforcement officers, and others who wish to identify prescription drugs not in this brochure, should contact the National Poison Control Hotline at 1-800-222-1222. By calling this number, you will be automatically connected to the drug and poison information center nearest you, who will assist in identifying the pill.

NOTICE

The tablets and capsules in this brochure are shown actual size. While every effort has been made to reproduce these drugs in an accurate manner, variations in color may exist because of the photographic reproduction and printing processes. Positive identification of any drug requires analysis by an authorized laboratory. The scheduling status of drugs shown are based on federal law, and may differ from individual state laws.

These brochures were made possible through a financial grant provided by Purdue Pharma L.P.

NADDI

1-888-39NADDI

www.naddi.org

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL PRESS RELEASE ("PPR")

Press Release dated 10/13/03, entitled "Tamper-Resistant Prescription Pads Offered to Michigan Physicians to Help Reduce Prescription Drug Diversion"

No. Artwork No. or Job. No.

Implementation Date: 10/13/03

PURDUE

Contact:
James Heins
(203) 588-8069

Tamper-Resistant Prescription Pads Offered to Michigan Physicians To Help Reduce Prescription Drug Diversion

STAMFORD, CT, October 13, 2003 – In an effort to help reduce the illegal diversion of prescription medications, pharmaceutical company Purdue Pharma L.P., the distributor of OxyContin® (oxycodone HCl controlled-release) Tablets, is providing doctors in Michigan with tamper-resistant prescription pads.

Prescription fraud – the alteration, forgery or counterfeiting of a physician's prescription – is a common source of diversion of controlled medications in the U.S. This free "Prescription Protection Program" is intended to help protect physicians, pharmacists, and patients from drug diverters who attempt to illegally obtain prescription medications. These pads employ six different security features designed to prevent tampering.

Through this voluntary program, physicians in Michigan can request an order form from their Purdue Pharma representative or call 1-877-887-9723 and order the prescription pads directly from the printer at no cost. A reputable carrier will deliver personalized prescription pads directly to the doctor, who must sign for the delivery personally.

Rep. Steve Ehardt (R-Lexington), Chair of the House Health Policy Committee and a registered pharmacist said, "This program supports the pharmacy profession's commitment to reduce drug diversion while helping to ensure that patients continue to have appropriate access to the medications they need to control chronic pain and other medical conditions."

Sen. Beverly Hammerstrom (R-Temperance), Chair of the Senate Health Policy Committee praised the efforts of Purdue Pharma L.P. in helping to stem the illegal diversion of prescription medications. "When a private company steps forward to voluntarily help fight a serious problem, and do it free of charge, I want to say thank you."

The program has been implemented in 34 states to date and more than 14,500 prescribers have ordered the tamper-resistant pads.

"The use of this technology should make it significantly more difficult for criminals to obtain controlled substances illegally without adding unnecessary barriers for patients with legitimate pain," says J. David Haddox, DDS, MD, Vice President, Health Policy with Purdue Pharma L.P.

The Prescription Protection Program is part of Purdue Pharma's 10-Point Program to reduce drug diversion and help ensure that legitimate patients continue to have appropriate access to the medication they need to control chronic pain and other medical conditions.

- more -

Purdue Pharma L.P., headquartered in Stamford, CT, is a privately held pharmaceutical company engaged in the research, development, production, sale, and licensing of both prescription and over-the-counter medicines and hospital products.

The professional product labeling for OxyContin® Tablets contains the following **boxed warning:**

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Full prescribing information for OxyContin is available at http://www.purduepharma.com/PRESSROOM/PI/OXYCONTIN_PI.PDF.

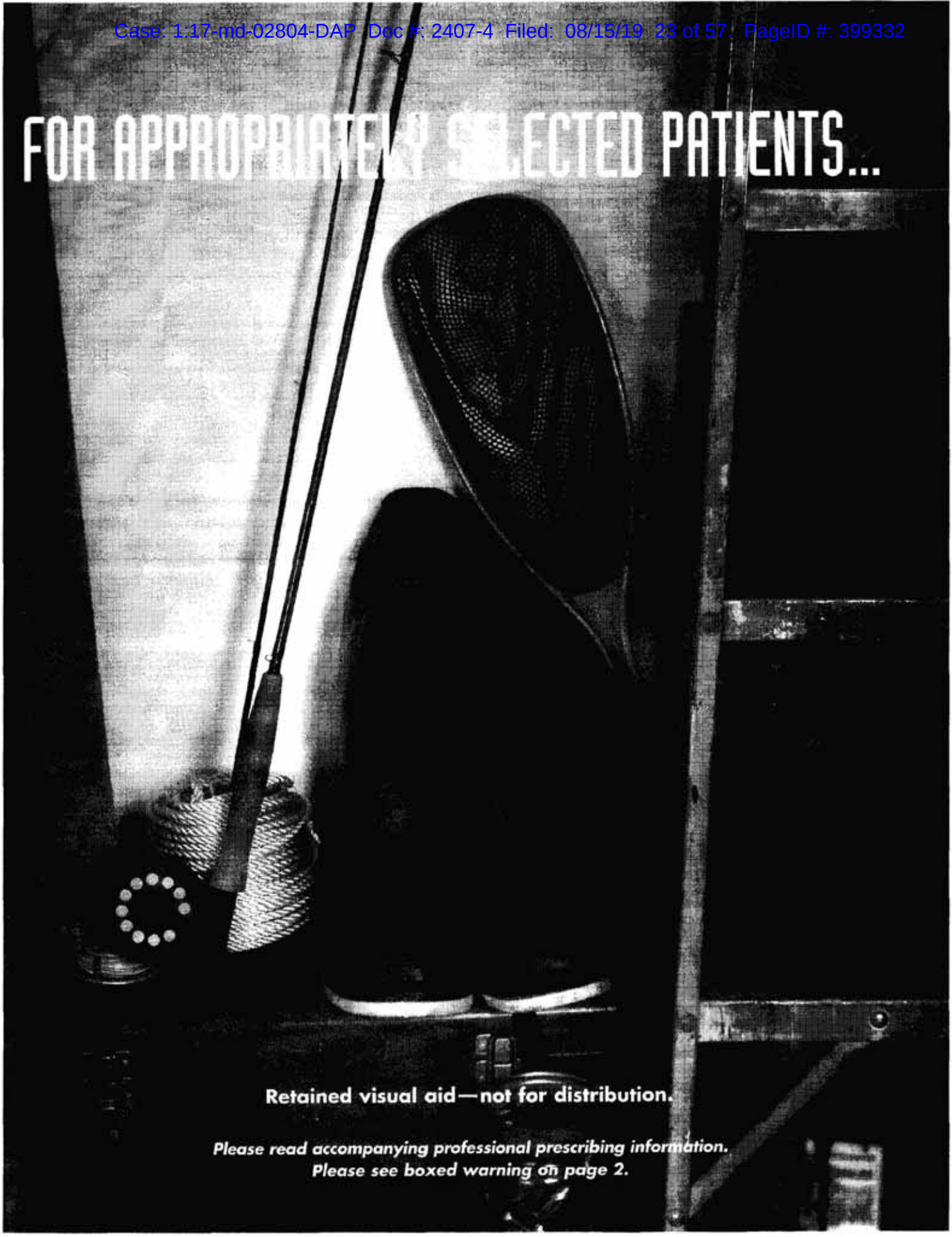
TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL SALES AID ("PSA")

OxyContin® Visual Aid:
"There Can Be Life with Relief"

Artwork No. D7072

Implementation Date: 10/29/03


FOR APPROPRIATELY SELECTED PATIENTS...
Retained visual aid—not for distribution.
Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

WARNING:

OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin® Tablets are NOT intended for use as a prn analgesic.

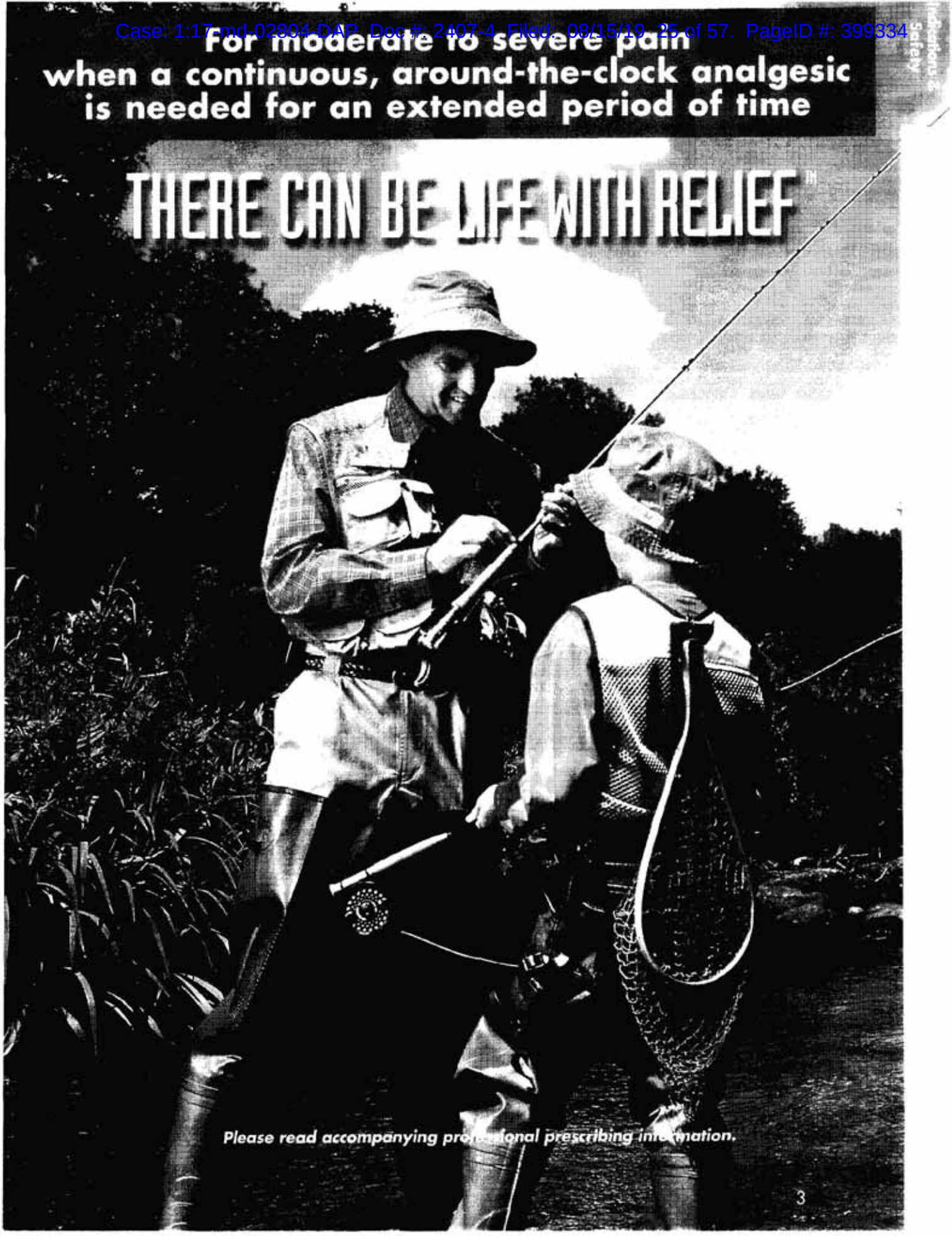
OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Indications and Usage

- OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
- As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort
- OxyContin® is **NOT** intended for use as a prn analgesic
- Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society
- OxyContin® is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time
- OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines)

Q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS


For moderate to severe pain
when a continuous, around-the-clock analgesic
is needed for an extended period of time
THERE CAN BE LIFE WITH RELIEF™
Please read accompanying professional prescribing information.
3

or moderate to severe pain when continuous, around-the-clock analgesic is eeded for an extended period of time

RELIEF FOR APPROPRIATE PATIENTS

Appropriate for use in moderate to severe pain when associated with conditions such as:

- Low back pain
- Osteoarthritis pain
- Postherpetic neuralgia pain
- Diabetic neuropathy pain
- Cancer pain
- Postoperative pain, only if the patient is receiving OxyContin® prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time
- As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort

What kind of patient is a candidate for OxyContin®?

- Persistent pain that is moderate to severe, requiring around-the-clock (ATC) therapy for an extended period of time

- Patients who are failing NSAIDs or COX-2 inhibitors and require ATC therapy
- Patients being considered for q4-6h opioids ATC

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

OxyContin® is not for everyone

- OxyContin® is **NOT** intended for use as a prn analgesic
- OxyContin® is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking OxyContin®, because its safety in this setting has not been established
- OxyContin® is not indicated for pain in the postoperative period that is mild or not expected to persist for an extended period of time
- OxyContin® is not indicated for pre-emptive analgesia (administration preoperatively for the management of postoperative pain)
- OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin® is contraindicated in any patient who has or is suspected of having paralytic ileus

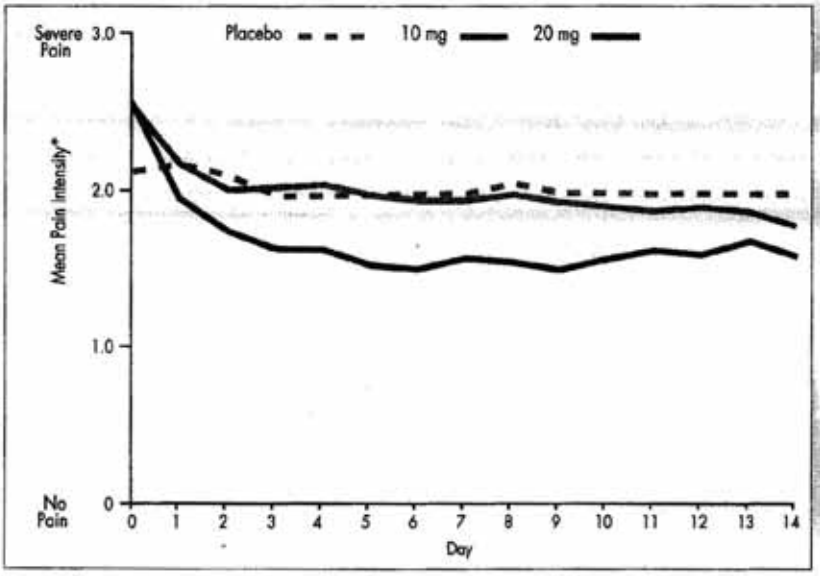
Q12h
OXYCONTIN® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

LIFE WITH EFFECTIVE RELIEF

Smooth and reliable pain control

Pain reduction in a placebo-controlled, fixed-dose trial of patients with moderate to severe osteoarthritis pain (n=133)[1]*



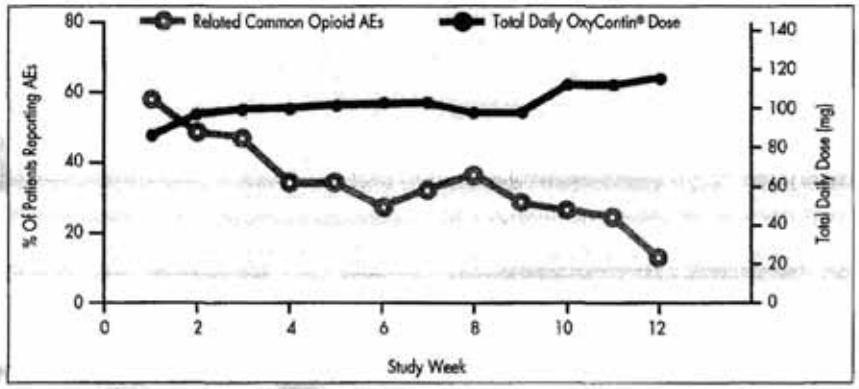
*Based on a 4-point categorical scale (0=no pain; 1=slight pain; 2=moderate pain; 3=severe pain).

- Prior to study, patients' pain was inadequately controlled with either prn opioids or NSAIDs
- OxyContin® 20 mg q12h provided significantly better pain control than placebo ($p<0.05$)[1]
- 10 mg q12h was similar to placebo in reducing pain intensity[1]
- Adverse events were more common with OxyContin® than with placebo[1]
- Common side effects include constipation, sedation, dizziness, vomiting, nausea, pruritus, headache, dry mouth, sweating, and weakness
- Frequently the side effects from OxyContin® (except constipation) are transient, but may require evaluation and management

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

Therapy-related adverse events

Therapy-related adverse events (AEs) and total daily OxyContin® dose (n=44)[2]



- Percentage of patients reporting common adverse effects decreased over the course of the study[2]
- Common opioid side effects (such as nausea, vomiting, somnolence, dizziness), except constipation, decreased over time in most patients[2]

Important risk information

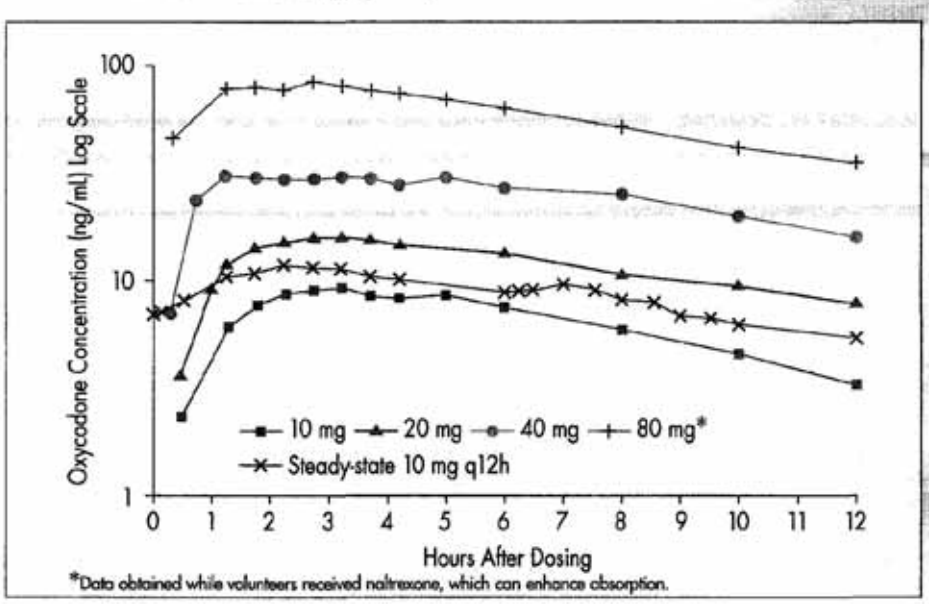
- **OxyContin® is a Schedule II controlled substance with an abuse liability similar to morphine.** Consider this when an increased risk of misuse, abuse, or diversion is a concern. See boxed warning on page 2.

Q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

CONSISTENT PLASMA LEVELS OVER 12 HOURS

Plasma concentrations (ng/mL) over time of various dosage strengths

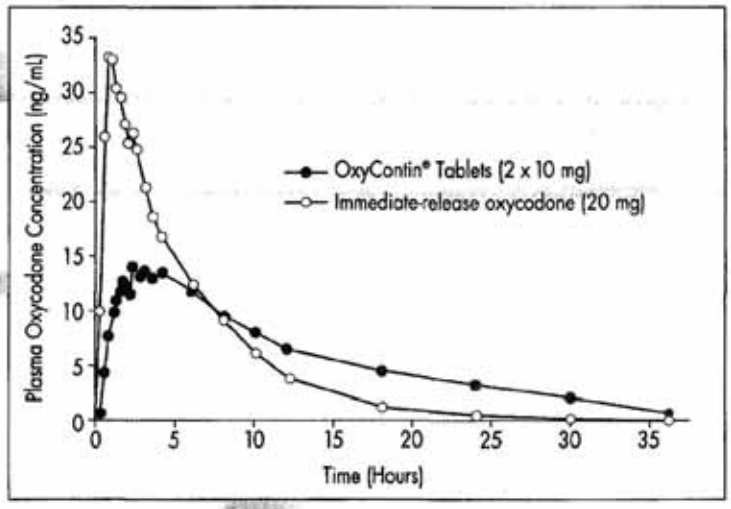


*Data obtained while volunteers received naltrexone, which can enhance absorption.

- Steady state achieved within 24 to 36 hours
- OxyContin® 80 and 160 mg Tablets FOR USE ONLY IN OPIOID-TOLERANT PATIENTS requiring minimum daily oxycodone equivalent dosages of 160 mg and 320 mg, respectively. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

Less fluctuation in plasma concentrations



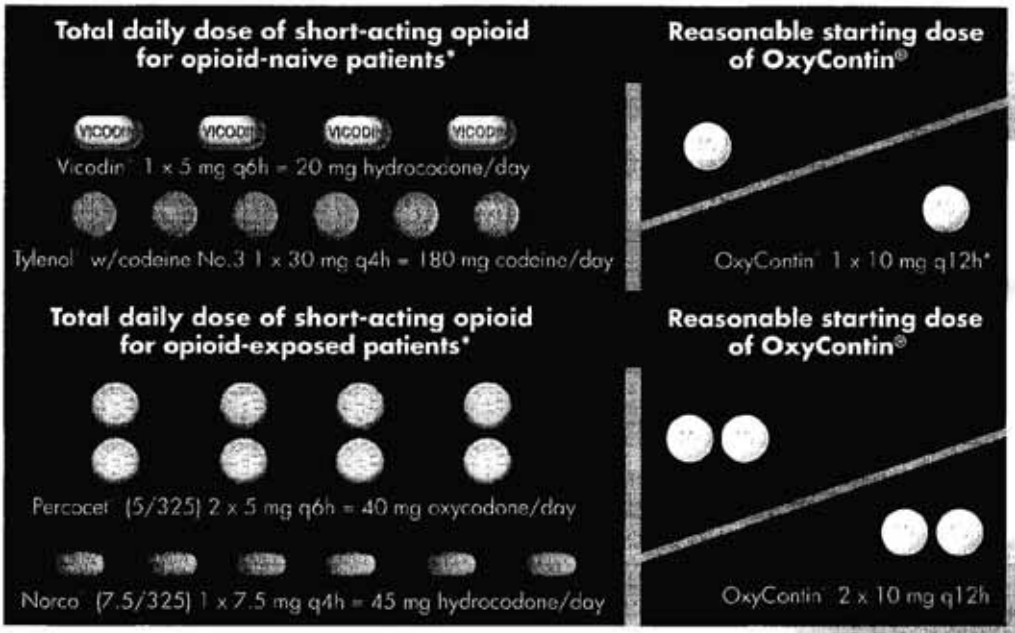
Mean plasma concentrations of oxycodone in normal volunteers after single doses of OxyContin® Tablets and immediate-release (IR) oxycodone[3]

- In a study comparing 10 mg of OxyContin® every 12 hours to 5 mg of IR oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations
- Less fluctuation in plasma concentrations with OxyContin® than with immediate-release oxycodone
- OxyContin® Tablets are to be swallowed whole, not broken, chewed, or crushed. Taking broken, chewed, or crushed tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone

Q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

LIFE WITH 2 DOSES, INSTEAD OF 4 OR 6



*When initiating OxyContin® therapy.

- These examples are based on conservative conversion ratios listed in the prescribing information. Treatment should be individualized based on physician discretion

Remember, effective relief takes just two

- Onset of analgesia within 1 hour in most patients[4†]
- Q12h OxyContin® is dosed less frequently than q4-6h opioid medications around-the-clock
- OxyContin® is **NOT** intended for use as a prn analgesic, or for pain that is mild, or not expected to persist for an extended period of time
- Asymmetrical dosing—the patient can use different dosing strengths for the first or second 12-hour period, depending on the pattern of pain

†From a single-dose study.

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

Consider the daily limitations

- Many short-acting opioids contain a non-opioid analgesic that limits the maximum daily dose

Examples:

Brand	Non-opioid component (mg)	Maximum recommended daily dosage of non-opioid	Maximum recommended dosage[a]
Vicodin ES®	Acetaminophen (750)	4 g[b]	5 tabs/day
Vicodin	Acetaminophen (500)	4 g[b]	8 tabs/day
Lortab® 5/500	Acetaminophen (500)	4 g[b]	8 tabs/day
Percocet 5/325	Acetaminophen (325)	4 g[b]	12 tabs/day
Percocet 10/650	Acetaminophen (650)	4 g[b]	6 tabs/day
Percodan®	Aspirin (325)	4 g[c]	12 tabs/day

Vicodin and Vicodin ES are registered trademarks of Abbott Laboratories. Tylenol is a registered trademark of Ortho-McNeil Pharmaceutical. Percocet and Percodan are registered trademarks of Endo Pharmaceuticals Inc. Norco is a registered trademark of Watson Laboratories, Inc. Lortab is a registered trademark of UCB Pharma.

- OxyContin® is a single-entity agent that does not contain acetaminophen, aspirin or ibuprofen
- Ceiling to analgesic effectiveness is limited only by side effects, the more serious of which may include somnolence and respiratory depression
- The most serious risk with OxyContin® is respiratory depression, which can be fatal

Q12h

OXYCONTIN® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

IT WORKS

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

LIFE WITH Q12H RELIEF

Convenient conversion from other opioids*

Multiplication factors for converting daily dose of prior oral pain medications to oral oxycodone

TOTAL DAILY DOSAGE OF CURRENT OPIOID MEDICATION

STEP 1: Multiply total by conversion factor below

CURRENT OPIOID	ORAL
Oxycodone	1.0
Codeine	0.15
Hydrocodone	0.9
Hydromorphone	4.0
Levorphanol	7.5
Meperidine	0.1
Methadone	1.5
Morphine	0.5

STEP 2: Divide by 2 to obtain q12h dose of OxyContin®

STEP 3: Round down to nearest dose of OxyContin® available

- OxyContin® is **NOT** intended for use as a prn analgesic
- Discontinue all other around-the-clock opioids before initiating treatment with OxyContin®
- When converting patients from non-opioid analgesics, OxyContin® 10 mg q12h is a reasonable starting dose
- Conversions listed as a general guide for clinicians. Treatment should be individualized for each patient at physician discretion
- A non-opioid analgesic may be continued as a separate drug, if needed
- For conversions from parenteral opioids or transdermal fentanyl, please see full prescribing information

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

Convenient conversion from short-acting opioids

*When initiating OxyContin® for patients previously taking opioids, the conservative conversion ratios from KM Foley (*N Engl J Med.* 1985;313:84-95) are a reasonable starting point, although not verified in well-controlled clinical trials.

All propoxyphene patients should be converted to 10 mg OxyContin® Tablets q12h.

†NOTE: Higher or more frequent doses exceed maximum recommended daily dosage.

Medication	Reasonable starting dosage of OxyContin®
Percocet® (5/325)	
1 tab q6h	10 mg q12h
1 tab q4h	10 mg q12h
2 tabs q6h	20 mg q12h
2 tabs q4h†	30 mg q12h
Vicodin® (5/500)	
1 tab q6h	10 mg q12h
1 tab q4h	10 mg q12h
Vicodin ES® (7.5/750)	
1 tab q6h†	10 mg q12h

- Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in nontolerant patients, or when opioids are given in conjunction with other agents that depress respiration
- As with all opioids, the starting dose should be reduced to ⅓ to ½ of the usual dosage in debilitated, nontolerant patients

Q12h

OXYCONTIN® CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

IT WORKS

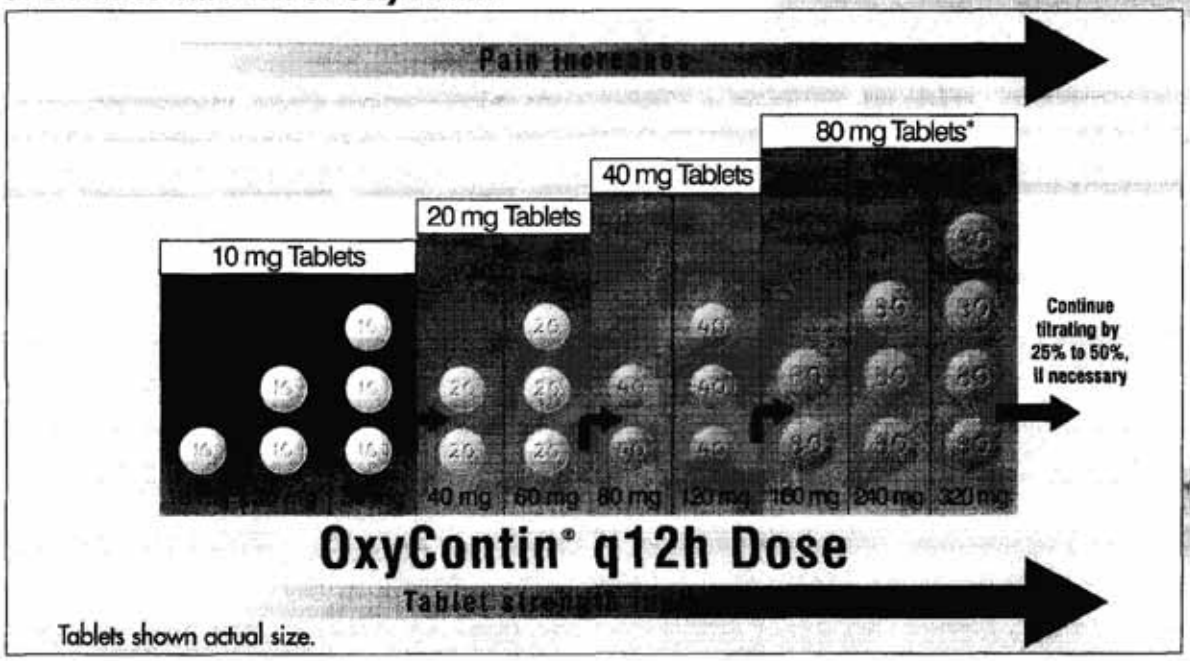
Small, color-coded tablets (actual size)

OxyContin® 80 and 160 mg Tablets FOR USE ONLY IN OPIOID-TOLERANT PATIENTS requiring minimum daily oxycodone equivalent dosages of 160 mg and 320 mg, respectively. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

LIFE WITH THE RELIEF PATIENTS NEED

A Guide to Titration of OxyContin®



*OxyContin® 80 and 160 mg Tablets FOR USE ONLY IN OPIOID-TOLERANT PATIENTS requiring minimum daily oxycodone equivalent dosages of 160 mg and 320 mg, respectively. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

- During periods of changing analgesic requirements (including initial titration), frequent contact is recommended between the physician, other healthcare team members, the patient and the caregiver/family

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

Adequate relief in T-I-M-E

T Titrate patients every 1 to 2 days, if necessary.

I Increase the dose of OxyContin® Tablets by 25% to 50%, if necessary (refer to the chart when titrating upward from 10 mg q12h). Do not increase the dosing frequency.

M Manage exacerbations of pain with immediate-release medication.

E Elevate the dose of OxyContin® Tablets if more than 2 doses of immediate-release opioid medication per day are required.

- The goal of titration is to effectively control pain with 2 or fewer rescue doses per day
- OxyContin® is **NOT** intended for use as a prn analgesic
- OxyContin® should be individually titrated to a dose that provides adequate analgesia and minimal side effects
- The need for around-the-clock opioid therapy should be reassessed periodically (eg, every 6 to 12 months) as appropriate for patients on chronic therapy
- Available in a variety of strengths, allowing you to titrate to an optimal dose

If the patient no longer requires OxyContin® therapy

- Taper doses gradually to prevent signs and symptoms of withdrawal in the physically dependent patient

Q12h
OXYCONTIN® II
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

APPROPRIATE RELIEF— FOR THE APPROPRIATE PATIENTS

OxyContin® is indicated for . . .

- Moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
- Postoperative use **only** if
  - The patient is already receiving the drug prior to surgery, **or**
  - Pain is expected to be moderate to severe and persist for an extended period of time

However, it is NOT indicated for . . .

- Use as a prn analgesic
- Pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking OxyContin®, because its safety in this setting has not been established
- Pain in the postoperative period that is mild or not expected to persist for an extended period of time
- Pre-emptive analgesia (administration preoperatively for the management of postoperative pain)
- Patients with known hypersensitivity to oxycodone
- When opioids are contraindicated, including patients with
  - Significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment)
  - Acute or severe bronchial asthma or hypercarbia
- Any patient who has or is suspected of having paralytic ileus

For more information, see **INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS** sections in the package insert.

Always individualize treatment in every case, by . . .

- Initiating therapy at the appropriate point along a progression from non-opioid analgesics to opioids in a plan of pain management such as outlined by the World Health Organization (WHO), Agency for Healthcare Research and Quality (AHRQ), Federation of State Medical Boards Model Guidelines, or American Pain Society (APS)
- Moving from parenteral to oral analgesics as appropriate (see APS guidelines)
- Using a progressive plan of pain management, such as outlined by the WHO, APS and the Federation of State Medical Boards Model Guidelines
- Following appropriate pain management principles of careful assessment and ongoing monitoring

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

Empower yourself against diversion

Misuse, abuse, and diversion of opioids

- OxyContin®, like other opioids, can be abused and is subject to criminal diversion. Specifically, it has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product
- These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death
- This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas and increased risk of endocarditis and valvular heart injury
- Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV

Protect yourself by keeping careful prescribing and treatment records,

including:

- Quantity
- Frequency
- Renewal requests
- Proper assessments of patients' pain
- Proper prescribing practices
- Periodic reevaluation of therapy

Educate patients on proper storage and disposal

- Instruct them to keep OxyContin® in a secure place, especially out of the reach of children
- When OxyContin® is no longer needed, dispose of unused tablets by flushing them down the toilet

Q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

Appropriate Use

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

IMPORTANT REMINDERS

Do not alter the tablet in any way

- **OxyContin® (oxycodone HCl controlled-release) Tablets CII are to be swallowed whole and are not to be broken, chewed, or crushed**
- **Taking broken, chewed, or crushed OxyContin® Tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone**

Use higher strengths ONLY when appropriate

- OxyContin® 80 and 160 mg Tablets FOR USE ONLY IN OPIOID-TOLERANT PATIENTS requiring minimum daily oxycodone equivalent dosages of 160 mg and 320 mg, respectively. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids
- Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death
- For more information, see **WARNINGS** section in the package insert

Please read accompanying professional prescribing information.
Please see boxed warning on page 2.

OxyContin® is not appropriate for:

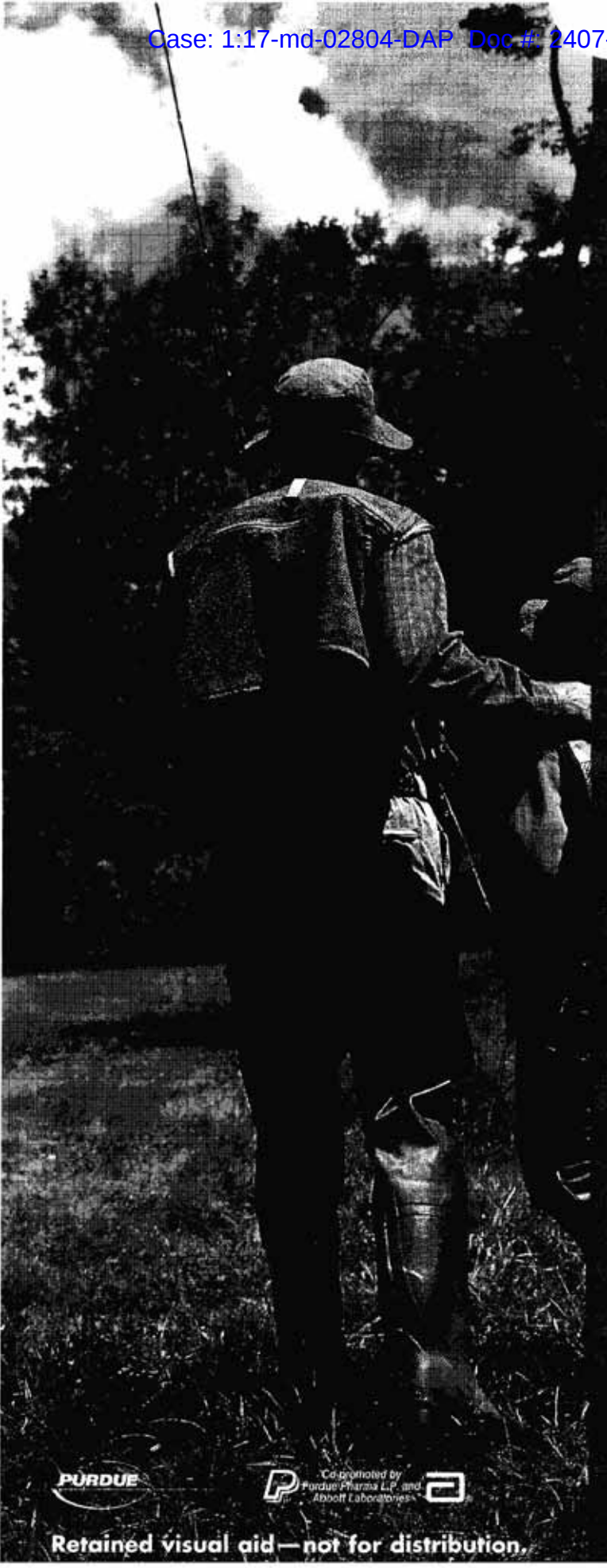
- Use as a prn analgesic
- Pre-emptive analgesia (administration preoperatively for the management of postoperative pain)
- Pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking OxyContin®, because its safety in this setting has not been established
- Pain in the postoperative period that is mild or not expected to persist for an extended period of time
- Patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin® is contraindicated in any patient who has or is suspected of having paralytic ileus

References: 1. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock controlled-release oxycodone therapy for osteoarthritis-related pain. *Arch Intern Med.* 2000;160:853-860. **2.** Citron ML, Kaplan R, Parris WC-V, et al. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain. *Cancer Invest.* 1998;16:562-571. **3.** Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol.* 1996;42:747-756. **4.** Sunshine A, Olson NZ, Colon A, et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. *J Clin Pharmacol.* 1996;36:595-603. **5.** Medical Economics Company Inc. Physicians' Desk Reference®, PDR® Electronic Library™ (see respective product names). Available at: http://www.pdrel.com. Accessed March 8, 2002. **6.** Roberts II LJ, Morrow JD. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill, Inc; 2001:687-731.

Purdue is firmly committed to maintaining the highest standards of marketing practices in the industry while continuing to advance the proper treatment of pain in America. If Purdue's marketing and sales practices fail to meet this standard, we urge you to contact us at **1-888-690-9211.**

Q12h
OXYCONTIN® (II)
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

Reminders



For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

THERE CAN BE LIFE WITH RELIEF®

OxyContin®...IT WORKS

- Effective relief of persistent, moderate to severe pain
- Q12h dosing convenience
- Onset of analgesia within 1 hour in most patients[4]*
- Convenient conversion and titration
- The most serious risk with OxyContin® is respiratory depression, which can be fatal
- OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin® is contraindicated in any patient who has or is suspected of having paralytic ileus
- **OxyContin® Tablets are to be swallowed whole, not broken, chewed, or crushed. Taking broken, chewed, or crushed tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone**
- **OxyContin® is a Schedule II controlled substance with an abuse liability similar to morphine.** Consider this when an increased risk of misuse, abuse, or diversion is a concern

*From a single-dose study.

Q12h

OxyContin® II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

IT WORKS

PURDUE

Co-promoted by Purdue Pharma L.P. and Abbott Laboratories

Please read accompanying professional prescribing information.

Please see boxed warning on page 2.

Retained visual aid—not for distribution.

OxyContin® CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg 20 mg 40 mg 80 mg* 160 mg*

*80 mg and 160 mg for use in opioid-tolerant patients only

07003670-811

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

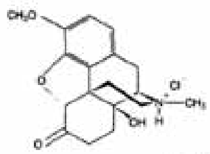
OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

[illegible]

CLINICAL PHARMACOLOGY

[illegible]

Central Nervous System

[illegible]

Gastrointestinal Tract and Other Smooth Muscle

[illegible]

Cardiovascular System

[illegible]

Concentration—Efficacy Relationships

[illegible]

Concentration—Adverse Experience Relationships

[illegible]

PHARMACOKINETICS AND METABOLISM

[illegible]

Absorption

[illegible]

Plasma Oxycodone by Time

[illegible]

dosing with OxyContin Tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin Tablets than for the immediate-release formulation.

Plasma Oxycodone By Time

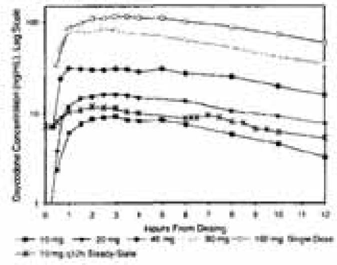


TABLE 1
Mean [% coefficient variation]

Regimen/ Dosage Form	AUC (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose				
10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose				
10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

TABLE 2
Mean [% coefficient variation]

Regimen/ Dosage Form	AUC_{∞} (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose				
4x40 mg OxyContin*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
2x80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
1x160 mg OxyContin*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

†for single-dose AUC = AUC_{0-inf}, for multiple-dose AUC = AUC_{0-T}

*data obtained while volunteers received naltrexone which can enhance absorption

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg Tablet was administered with a high-fat meal.

Distribution

[illegible]

Metabolism

[illegible]

Excretion

[illegible]

Special Populations

Elderly

[illegible]

Gender

[illegible]

Renal Impairment

[illegible]

Hepatic Impairment

[illegible]

Drug-Drug Interactions (see **PRECAUTIONS**)

[illegible]

Pharmacodynamics

[illegible]

CLINICAL TRIALS

[illegible]

INDICATIONS AND USAGE

[illegible]

OxyContin is **NOT** intended for use as a prn analgesic.

[illegible]

CONTRAINDICATIONS

[illegible]

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. [illegible]

[illegible]

Misuse, Abuse and Diversion of Opioids

[illegible]

Interactions with Alcohol and Drugs of Abuse

[illegible]

DRUG ABUSE AND ADDICTION

[illegible]

Respiratory Depression

[illegible]

Head Injury

[illegible]

Hypotensive Effect

[illegible]

PRECAUTIONS

General

[illegible]

Interactions with other CNS Depressants

[illegible]

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

[illegible]

Ambulatory Surgery and Postoperative Use

[illegible]

Use in Pancreatic/Biliary Tract Disease

[illegible]

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes (in the absence of metabolic activation at doses of up to 1500 μg/mL and with activation 48 hours after exposure at doses of up to 5000 μg/mL), and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 μg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/mL or greater with metabolic activation and at 400 μg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects — Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	OxyContin (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	—
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain, and symptoms associated with either an anaphylactic or anaphylactoid reaction

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCONTIN® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **BOXED WARNING**).

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;

(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;

(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;

(4) the patient's opioid exposure and opioid tolerance (if any);

(5) special safety issues associated with conversion to OxyContin® doses at or exceeding 160 mg q12h (see **Special Instructions for OxyContin 80 mg and 160 mg Tablets**); and

(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Foley, KM. (NEJM, 1985; 313:84-95), found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*

(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

***To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia should be made available in the form of a suitable short-acting analgesic.

OxyContin® can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 μg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for OxyContin 80 mg and 160 mg Tablets

(For use in opioid-tolerant patients only)

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One OxyContin® 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-100-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-103-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-105-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-107-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 160 mg are caplet-shaped, unscored, blue-colored, convex tablets imprinted with OC on one side and 160 on the other. They are supplied as follows:

NDC 59011-109-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-109-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

Purdue Pharma L.P., Stamford, CT 06901-3431

U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295

July 30, 2003 [illegible] OP[illegible]

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

INTERNET PROMOTION ("WWW")

Site Navigation for OxyContin® Information in "Newsroom" of Purdue's Corporate Website

No Artwork No. or Job No.

Implementation Date: 4/17/03

- Company News
- OxyContin® Tablets Information
  - Press Releases
- Media Contacts

News & Announcements - OxyContin® (Oxycodone HCl Controlled-Release) Tablets Information

Kentucky Federal Judge Dismisses OxyContin® Case	03/19/2003
Five OxyContin® Cases Against Purdue Pharma Dismissed	02/26/2003
Statement on DDMAC Warning Letter	01/22/2003
Purdue Product Replacement Program	01/21/2003
Thousands of Counterfeit OxyContin® Tablets Seized by U.S. Customs Service	12/04/2002
Purdue Pharma Announces New Initiatives with Florida Attorney General to Combat Illegal Trafficking and Abuse of Prescription Medicines	11/01/2002
Boston Area Residents Urged To Report Information On Pharmacy Robbers Click Here to Hear Audio	10/24/2002

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PROFESSIONAL PRICE CATALOG ("PCT")

Current Purdue Wholesaler Pricing Schedule

Dated: 9/9/03

WHOLESALER
PRICING SCHEDULE

EFFECTIVE SEPTEMBER 9, 2003

PURDUE
One Stamford Forum
Stamford, CT 06901-3431

PRODUCT	NDC#	UNIT SIZE	UNIT COST	ORDER IN MULTIPLES OF	CASE SIZE	CASE COST
PURDUE PHARMA L.P.						
OXYCONTIN TABLETS C-II...Rx **(Oxycodone HCl, Controlled-Release) **Warning:** May be Habit Forming.	59011-100-10	1 bottle of 100 tablets (10 mg.)	$115.04	6	6 x 100 tablets	$690.24
	59011-103-10	1 bottle of 100 tablets (20 mg.)	$220.13	6	6 x 100 tablets	$1,320.78
	59011-105-10	1 bottle of 100 tablets (40 mg.)	$390.59	6	6 x 100 tablets	$2,343.54
	59011-107-10	1 bottle of 100 tablets (80 mg.)	$734.51	6	6 x 100 tablets	$4,407.06
	59011-109-10	1 bottle of 100 tablets (160 mg.)	$1,384.96	6	6 x 100 tablets	$8,309.76
OXYCONTIN TABLETS C-II...Rx UNIT DOSE **(Oxycodone HCl, Controlled-Release) **Warning:** May Be Habit Forming.	59011-100-25	1 card of 25 tablets (10 mg.)	$31.27	12	300 tablets (12/25s)	$375.24
	59011-103-25	1 card of 25 tablets (20 mg.)	$59.85	12	300 tablets (12/25s)	$718.20
	59011-105-25	1 card of 25 tablets (40 mg.)	$106.11	12	300 tablets (12/25s)	$1,273.32
	59011-107-25	1 card of 25 tablets (80 mg.)	$199.66	12	300 tablets (12/25s)	$2,395.92
	59011-109-25	1 card of 25 tablets (160 mg.)	368.34	4	100 tablets (4/25s)	1473.36

** DEA Order Form 222-C Required.

TRANSMITTAL OF ADVERTISEMENTS
AND PROMOTIONAL LABELING FOR
DRUGS FOR HUMAN USE
Product: OxyContin® (oxycodone hydrochloride) Tablets
NDA #: 20-553

PACKAGE INSERT

OxyContin® Tablets

Version OT00367D-E

Dated: 7/30/03

OxyContin® II
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
10 mg 20 mg 40 mg 80 mg* 160 mg*
*80 mg and 160 mg for use in opioid tolerant patients only.

OT003670-E 00P017

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

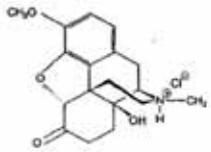
OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.

The 10 mg tablets also contain: hydroxypropyl cellulose.

The 20 mg tablets also contain: polysorbate 80 and red iron oxide.

The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.

The 80 mg tablets also contain: FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

The 160 mg tablets also contain: FD&C blue No. 2 and polysorbate 80.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of OxyContin® overdose (See **OVERDOSAGE**).

Gastrointestinal Tract And Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall 'drug effect', analgesia and feelings of 'relaxation'.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Experience Relationships

OxyContin® Tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of OxyContin Tablets is primarily due to the parent drug oxycodone. OxyContin Tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing OxyContin Tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin Tablets is pH independent. Oxycodone is well absorbed from OxyContin Tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral

dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin® was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the $t^1/_2$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin Tablets exhibit a biphasic absorption pattern with two apparent absorption half-lives of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from OxyContin®, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin Tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin Tablets than for the immediate-release formulation.

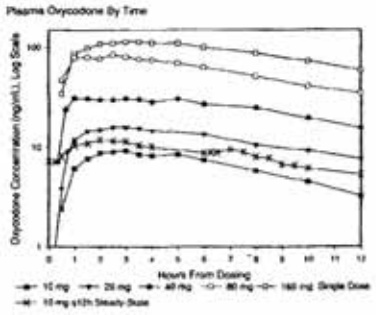


TABLE 1

Mean [% coefficient variation]

Regimen/ Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose				
10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose				
10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

TABLE 2

Mean [% coefficient variation]

Regimen/ Dosage Form	AUC $_{\infty}$ (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose				
4x40 mg OxyContin*	1335.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
2x80 mg OxyContin*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
1x160 mg OxyContin*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

†for single-dose AUC=$AUC_{0-\infty}$; for multiple-dose AUC=AUC_{0-t}

*data obtained while volunteers received naltrexone which can enhance absorption.

OxyContin® is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg Tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t^1/_2$ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The $t^1/_2$ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin®

(10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of OxyContin were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg OxyContin q12h but not 10 mg OxyContin q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin is **NOT** intended for use as a prn analgesic. Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

'Drug-seeking' behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated 'loss' of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). 'Doctor shopping' to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin®, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources

of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (⅓ to ½ of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix 'ghosts' (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach

of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction
OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions
Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants
OxyContin®, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 μg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 μg/mL and with activation 48 hours after exposure at doses of up to 5000 μg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 μg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 μg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 μg/mL or greater with metabolic activation and at 400 μg/mL or greater without metabolic activation.

Pregnancy
Teratogenic Effects — Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers
Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use
Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

Geriatric Use
In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring
Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment
A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment
In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences
In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS
The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.
In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.
Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin

and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	OxyContin (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	—
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain, and symptoms associated with either an anaphylactic or anaphylactoid reaction

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin®, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See **BOXED WARNING**].

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;

(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;

(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;

(4) the patient's opioid exposure and opioid tolerance (if any);

(5) special safety issues associated with conversion to OxyContin® doses at or exceeding 160 mg q12h (see **Special instructions for OxyContin 80 mg and 160 mg Tablets**); and

(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.

2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*

(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

***To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia should be made available in the form of a suitable short-acting analgesic.

OxyContin® can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 μg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalites may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for OxyContin® 80 mg and 160 mg Tablets (For use in opioid-tolerant patients only.)

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One OxyContin® 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin® Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-100-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-

release) Tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-103-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-105-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-107-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) Tablets 160 mg are caplet-shaped, unscored, blue-colored, convex tablets imprinted with OC on one side and 160 on the other. They are supplied as follows:

NDC 59011-109-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-109-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

Purdue Pharma L.P., Stamford, CT 06901-3431

U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295

July 30, 2003 OT00367D-E 00P017